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Rec'd PCT/PTO 30 SEP 2004

REC'D 18 JUL 2003
WIPO PCT

सत्यमेव जयते

INTELLECTUAL
PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

*I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the Application and Complete Specification filed in connection with Application for Patent No.**425/Del/02** dated 3rd **April 2002**.*

Witness my hand this 12th Day of May 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

26 MAR 2003

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

25/pd/02
3-4-02

(See Sections 7, 54 and 135 and rule 33A)

We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"IMPROVED DISSOLUTION AND BIOAVAILABILITY OF CLARITHROMYCIN HAVING REDUCED PARTICLE SIZE FROM EXTENDED RELEASE FORMULATIONS"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. ASHOK RAMPAL

b. RAJEEV S. RAGHUVANSHI

c. MANOJ KUMAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

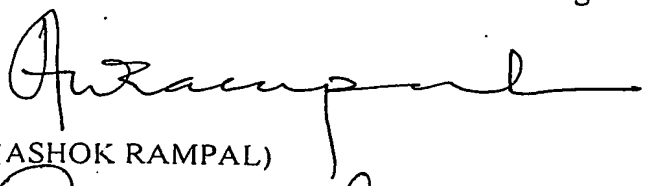
4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

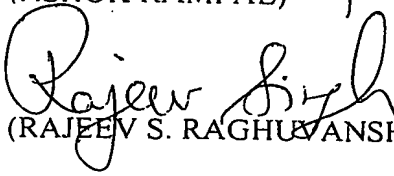
DR. B. VIJAYARAGHAVAN
Group Leader – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, ASHOK RAMPAL; RAJEEV S. RAGHUVANSHI; MANOJ KUMAR of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. 

(ASHOK RAMPAL)

b. 

(RAJEEV S. RAGHUVANSHI)

c.

(MANOJ KUMAR)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3

We request that a patent may be granted to us for the said invention.

Dated this **25TH** day of **March, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

IMPROVED DISSOLUTION AND BIOAVAILABILITY OF CLARITHROMYCIN HAVING REDUCED PARTICLE SIZE FROM EXTENDED RELEASE FORMULATIONS

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

This invention relates to a solid pharmaceutical composition of clarithromycin with enhanced absorption and dissolution characteristics. Further it also relates to a process for preparing such a dosage form.

There is a constant need in the pharmaceutical industry for improved pharmaceutical formulations which enhance the efficacy of poorly soluble therapeutic agents. There is especially a need for formulations that (1) enhance the absorption of poorly soluble therapeutic agents, and (2) extend the period of duration of effect.

The aqueous solubility of drug substance plays an important role in the performance of dosage forms. For the oral route of administration it is well experienced that, unless the substance has an aqueous solubility above 10mg/ml over the pH range 1-7, potential absorption problems may occur. Numerous active ingredients suffer from the disadvantage of being poorly soluble in an aqueous medium, thus having an insufficient dissolution profile and consequently, poor bioavailability following oral administration. The therapeutic dose required to be administered must be increased in order to obviate this disadvantage. This necessitates the administration of active ingredients three or four times a day in order to achieve the desired effect.

For a drug which is administered in multiple doses, it is reported that the patient compliance is a high as 87% when administered once a day as when compared to 39% for a q.i.d. dosage regimen. This suggests that an extended-release dosage form would improve the quality of therapy and the safety profile relative to a conventional dosage form. However, in order to be effective, it is important that these extended release formulations completely release the drug within a predetermined period.

Erythromycin and its derivatives are known for their antibacterial activity against a number of organisms and are typically administered two to three times a day as immediate release compositions. In particular, 6-0-methoxyerythromycin A (clarithromycin) which has been disclosed in US Patent No. 4,331,803 has to be administered at least twice daily for optimal effect.

Clarithromycin presents a peculiar problem for the formulator as it has greater solubility but very low stability at the acidic pH conditions in stomach, and while its stability is good at alkaline pH of lower portion of the intestine (pH 6.0 to 8.0), its solubility is poor there. This results in poor bioavailability of clarithromycin.

It is therefore desirable to develop a dosage form of clarithromycin having an improved dissolution and absorption characteristics and which can be administered once a day.

We have surprisingly found that the dissolution and absorption characteristics of clarithromycin as also its bioavailability can be increased with micronization of clarithromycin.

The term "micronization" used herein means any process or methods by which the size of the particles is reduced and clarithromycin particles with reduced size are referred to as "micronized particles of clarithromycin" or "micronized clarithromycin".

Therefore in one general aspect invention relates to micronized particles of clarithromycin, having an improved dissolution and absorption characteristics.

In one general aspect, a solid formulation of clarithromycin is provided, comprising micronized clarithromycin, which exhibits improved dissolution and absorption characteristics.

In another general aspect, a solid formulation of clarithromycin is provided, comprising micronized clarithromycin in a daily dosage amount of about 100mg to 1000 mg, which exhibits improved dissolution and absorption characteristics.

According to another general aspect, an extended release solid formulation of clarithromycin is provided, which comprises micronized clarithromycin particles and exhibits improved dissolution and absorption characteristics.

According to another general aspect, an extended release solid formulation of clarithromycin is provided, which comprises clarithromycin particles having a particle

size less than 35 microns and exhibits improved dissolution and absorption characteristics.

According to yet another general aspect, an extended release solid formulation of clarithromycin is provided which comprises:

(a) micronized clarithromycin,

(b) rate-controlling polymers, and

(c) pharmaceutically acceptable excipients

wherein the formulation exhibits improved dissolution and absorption characteristics.

According to another general aspect, an extended release solid formulation of clarithromycin comprises:

(a) micronized clarithromycin having a particle size less than 35 microns,

(b) rate-controlling polymers, and

(c) pharmaceutically acceptable excipients

wherein the formulation exhibits improved dissolution and absorption characteristics.

According to another general aspect, a once a day solid formulation of clarithromycin comprises:

(a) micronized clarithromycin,

(b) rate-controlling polymers, and

(c) pharmaceutically acceptable excipients

wherein the formulation exhibits improved dissolution and absorption characteristics.

According to another general aspect, a once a day solid formulation of clarithromycin comprises:

(a) micronized clarithromycin having a particle size less than 35 microns,

(b) rate-controlling polymers, and

(c) pharmaceutically acceptable excipients

wherein the formulation exhibits improved dissolution and absorption characteristics.

In another general aspect, a process is provided for preparing a solid formulation of clarithromycin with improved dissolution and absorption.

In another general aspect it relates to a process for preparing a solid formulation of clarithromycin with improved dissolution and absorption characteristics comprising the step of micronization of clarithromycin.

The clarithromycin can be prepared by any available method, as for example it may be prepared by the procedure disclosed in U.S. Pat. No. 4,331,803, or the procedure disclosed in U.S. Pat. No. 4,672,109, both herein incorporated by reference.

Size reduction or micronization may be carried out in any of the conventionally known mills, such as ball mill, colloid mill, grinding mill, air jet mill, roller mill, impact mill, etc. More particularly air jet milling is used as it is a well proven technique that consistently produces particles of size less than 35 microns. The primary advantage of air jet milling is that particle size reduction occurs via particle to particle collisions with limited reduction from metal to product contact and no generation of heat.

The process of air jet milling comprises exposing the material to be micronized, to streams of compressed air or gas. Particles in the fluidized bed created by the gas streams are accelerated towards the center of the mill colliding with the slower moving particles. The air jet mills operate by applying opposing air flows and centrifugal forces. By balancing the two forces, smaller and larger particles can be separated.

The reduction of the particle size of clarithromycin to a D_{90} particle size of less than 35 microns result in improved bioavailability of clarithromycin pharmaceutical compositions as compared to bigger particle size clarithromycin containing pharmaceutical compositions. Clarithromycin particles having a D_{90} particle size of less than about 35 microns are referred to herein as micronized clarithromycin particles.

As used herein, D_{90} particle size is the particle size of at least 90% of the particles of clarithromycin used in the composition.

In another general aspect it relates to a process for preparing a solid formulation of clarithromycin with improved dissolution and absorption characteristics comprising the step of micronization of clarithromycin; and forming a finished dosage form.

In another general aspect it relates to a process for preparing a solid formulation of clarithromycin with improved dissolution and absorption characteristics comprising the step of micronization of clarithromycin with pharmaceutically inert carrier(s).

In another general aspect it relates to a process for preparing a solid formulation of clarithromycin with improved dissolution and absorption characteristics comprising the step of micronization of clarithromycin with pharmaceutically inert carrier(s); and forming a finished dosage form.

In another general aspect it relates to a process for preparing a solid formulation of clarithromycin with improved dissolution and absorption characteristics comprising the step of micronization of clarithromycin; and forming a tablet.

In another general aspect it relates to a process for preparing a solid formulation of clarithromycin with improved dissolution and absorption characteristics comprising the step of micronization of clarithromycin with pharmaceutically inert carrier(s); and forming a tablet.

As used herein, the term "pharmaceutically inert carrier" refers to a substance, which is physiologically acceptable and compatible with the drug and other excipients in the formulation and has a capacity to adsorb the drug on its surface. Carriers prevent reagglomeration of drug particles and also help in wetting of drug, involving the uptake of water by capillary action and thereby enhancing drug dissolution further.

The pharmaceutically inert carrier may be selected from cellulose derivatives like microcrystalline cellulose, carboxymethyl cellulose; silicate derivatives like magnesium silicate, colloidal silicon dioxide magnesium trisilicate, magnesium aluminium silicate; and clays like veegum, bentonite, etc.

Rate-controlling polymers comprise of carbohydrate gum, polyuronic acid salts, cellulose ethers, acrylic acid polymers and mixtures, thereof.

Carbohydrate gums may be selected from amongst xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan, locust bean gum and the like.

Polyuronic acid salts include alkali metal salts of alginic acid or pectic acid and mixtures thereof. Examples of alkali metal salts of alginic acid that may be used include sodium alginate, potassium alginate, ammonium alginate and the like.

Cellulose ethers include hydroxypropyl methyl cellulose, hydroxypropyl cellulose and the like.

Polyacrylic acid polymers may be such as is available under the brand name carbopol.

In addition to the rate controlling polymers, the composition may additionally comprise of other pharmaceutically acceptable excipients such as gas generating components, swelling agents, lubricants and fillers.

Gas generating components may include carbonates, such as calcium carbonate, bicarbonates such as sodium bicarbonate; sulfites such as sodium sulfite and the like.

Swelling agents may include cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl cellulose sodium, sodium starch glycolate and the like.

Lubricants may be selected from talc, calcium stearate, magnesium stearate, polyethylene glycols, silicon dioxide, sodium lauryl sulphate, sodium stearyl fumarate and mixtures thereof.

The following examples illustrate the invention without limiting it.

EXAMPLE 1

PREPRATION OF EXTENDED RELEASE TABLET FORMULATION OF CLARITHROMYCIN

Ingredients	Mg/tablet
Clarithromycin micronized (Particle size: D_{90}=31.93 microns)	1000.0
Hydroxypropyl methylcellulose K15M	10.0
Hydroxypropyl methylcellulose K4M	17.5
Polyvinyl pyrrolidone K-30	25.0
Lactose	50.0
Magnesium stearate	12.5
Talc	10.0
Sodium stearyl fumarate	20.0
Colloidal silicon dioxide	5.0
Total weight	**1150.0**

Clarithromycin (micronized), hydroxypropyl methylcellulose K15M, hydroxypropyl methylcellulose K4M, polyvinyl pyrrolidone K30 and lactose were sieved through a British Standard Sieve (BSS) 44 mesh sieve and blended together followed by granulation with water. The granulate was dried in a fluid bed drier at 60°C for 20 minutes. The dried granules were sifted through a BSS 16 mesh sieve. The granules obtained were lubricated with the remaining ingredients and compressed to tablets.

EXAMPLE 2

Effect of particle size on the in-vitro drug release profile of clarithromycin extended release tablet prepared as per the composition of Example 1 using two different particle sizes, one micronized (D_{90}=29.73 microns) and another unmicronized (D_{90}=246.39 microns) is shown in Table-1.

Table 1: Dissolution profile of clarithromycin extended release pharmaceutical compositions prepared with clarithromycin particles of different sizes carried out in USP apparatus II/1000ml/pH4.0, mixed phosphate buffer/80 rpm.

Time (hr)	Percent (%) drug released	
	Particle size	
	D_{90}=29.73 microns	D_{90}=246.39 microns
1	14	12
2	30	20
4	59	33
8	99	59
10	103	70

EXAMPLE 3

Bioavailability study: The extended release clarithromycin solid formulation of Example 1 having clarithromycin with mean particle size of D_{90} equivalent to 31.93 microns was subjected to bioavailability study while comparing with commercially available tablets Biaxin film tab 500mg b.i.d. (Abbott).

The bioavailability study was done on six healthy subjects. It was conducted as single dose, open, randomized, balanced, crossover study under fed conditions.

Blood samples were drawn at selected times following each treatment. Blood levels of the drug for both test and reference were determined and compared for Area Under the plasma concentration – time curve (AUC).

Test : Extended release clarithromycin formulation made according to Example 1 and comprising clarithromycin with a particle size of D_{90} equivalent to 31.93 microns.

Reference : Commercially available clarithromycin formulations (Biaxin Filmtab 500mg administered twice daily.

The results are shown in Table 2.

Table 2

Formulation		AUC 0-24h (μg.hr/ml)	T/R
Biaxin Filmtab 500mg (R)	b.i.d	37.95	-
	First dose	16.9	-
Clarithromycin XL (T)	1000 mg	36.6	96.4%
	Interpolated value for 500 mg	18.3	108.3%

EXAMPLE 4

Preparation of extended release pharmaceutical formulation of clarithromycin with mean particle size of D_{90}-equivalent to 275.58 microns.

Ingredients	Mg/tablet
Clarithromycin	500
Lactose	117
Hydroxypropyl cellulose-L	105
Hydroxypropyl cellulose – M	125
Polyvinyl pyrrolidone K 30	10
Talc	18
Sodium stearyl fumarate	18
Colloidal silicon dioxide	2
Magnesium stearate	5

Clarithromycin, hydroxypropyl cellulose M, hydroxypropyl cellulose L, polyvinyl pyrrolidone K30 and lactose were sieved through a British Standard Sieve (BSS) 44 mesh sieve and blended together followed by granulation with water. The granulate was dried in a fluid bed drier at 60°C for 20 minutes. The dried granules were sifted

through a BSS 16 mesh sieve. The granules obtained were lubricated with the remaining ingredients and compressed to tablets.

The extended release clarithromycin formulation of Example 4 having clarithromycin with mean particle size of D_{90} equivalent to 275.58 microns was subjected to bioavailability study while comparing with commercially available tablets, Klaricid XL tablets, 500mg (Abbott).
The study was conducted in twelve healthy subjects as single dose, open, randomized, balanced crossover study.

Test : Extended release clarithromycin formulation (500mg) made according to Example 4 and comprising clarithromycin with a particle size of D_{90} equivalent to 275.58 microns.

Reference : Commercially available clarithromycin extended release tablets (Klaricid XL 500mg)

The results of the study are presented in Table 3.

Table 3

AUC 0-24h (μg.hr/ml)		T/R
Test	**Reference**	
13.0	17.72	73.36%

WE CLAIM:

1. A process for preparing a solid pharmaceutical composition of clarithromycin, comprising micronized clarithromycin, which exhibits improved dissolution and absorption characteristics.
2. The process according to claim 1 wherein clarithromycin has a particle size less than 35 microns.
3. The process according to claim 1 or 2 wherein the pharmaceutical composition is an extended release formulation.
4. The process according to claim 1 or 2 wherein the pharmaceutical composition is a once a day formulation.
5. The process according to claim 1 or 2 wherein the dosage form is a tablet or a capsule.
6. The process according to claim 5 wherein the dosage form is a tablet.
7. The process according to claim 1 wherein clarithromycin is micronized in air jet mill.
8. The process according to claim 1 wherein clarithromycin is co-micronized with pharmaceutical inert carrier(s).
9. The process according to claim 8 wherein pharmaceutically inert carrier may be selected from cellulose derivatives, silicate derivatives and clays.
10. The process according to claim 9 wherein the cellulose derivative is microcrystalline cellulose, carboxymethyl cellulose and the like.
11. The process according to claim 9 wherein the silicate derivative is magnesium silicate, colloidal silicon dioxide, magnesium trisilicate, magnesium aluminicum silicate and the like.
12. The process according to claim 9 wherein clay is veegum, bentonite and the like.
13. The process according to claim 9 wherein amount of pharmaceutically inert carrier is about 2% to 25% by weight relative to the total weight of the formulation.

14. The process according to claim 3 or 4 wherein the formulation comprises:
    (a) micronized clarithromycin,
    (b) rate-controlling polymers, and
    (c) pharmaceutically acceptable excipients,
    and exhibits improved dissolution and absorption characteristics.

15. The process according to claim 14 wherein the rate controlling polymers are selected from carbohydrate gums, polyuronic acid salts, cellulose ethers, acrylic acid polymers and mixtures thereof.

16. The process according to claim 15 wherein carbohydrate gums are selected from xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan, locust bean gum and the like.

17. The process according to claim 15 wherein polyuronic acid salts are selected from alkali metal salts of alginic acid or pectic acid.

18. The process according to claim 15 wherein cellulose ethers are selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose and the like.

19. The process according to claim 15 wherein polyacrylic polymers may be such as those available under the brand name carbopol.

20. The process according to claim 14 wherein pharmaceutically acceptable excipients are selected from gas generating components, swelling agents, lubricants and fillers.

21. The process according to claim 1 wherein the pharmaceutical composition has area-under-the-curve (AUC) comparable to the area-under-the-curve (AUC) of commercially available twice-daily immediate release dosage form.

22. A process for improving bioavailability of clarithromycin as described and illustrated by the examples herein.

Dated this **25TH** day of **March, 2003**.

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

This invention relates to a solid pharmaceutical composition of clarithromycin, comprising micronized clarithromycin, with enhanced absorption and dissolution characteristics. Further it also relates to a process for preparing such a dosage form.